Neuronal Inihibition Induces Downregulation of Flow and Metabolism

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Introduction Sustained decreases in the BOLD signal have been reported in a number of visual [2,6] and motor studies [5] and postulated to result from the purely hemodynamic effect of "blood stealing" and/or neuronal inhibition [6]. In the present study, we investigated the hemodynamic and metabolic processes concomitant to the steady-state negative BOLD response induced by a low force, phasic pinch grip task [1] and thus originating from transcallosal inhibition according to extensive evidence from transcranial magnetic stimulation (TMS) studies.

Methods The scanning protocol consisted of a 1x1x2mm^3 3D RF-spoiled T_1-weighted gradient echo sequence (TR/TE of 22/10 ms) for anatomical reference, followed by interleaved multi-slice PASL and T_2-weighted gradient echo sequence for CBF and BOLD signal measurements (TR of 2.5 s and TE of 22/50 ms for CBF/BOLD). The latter acquisitions covered 7 slices (4x4x7 mm^3*;* inter-slice gap of 0.7 mm) parallel to the AC-PC line, with the seventh slice grazing the top of the brain. A PICORE labeling scheme was employed with 2 presaturation pulses in the imaging region followed by an adiabatic FOCI inversion in the labeling region (100 mm thickness, with a gap of 5 mm) and a post-label delay of TI=1.2 s. Eight healthy, right-handed adults (28±3yrs) performed the pinch grip at a frequency of 1 Hz (with 12 20s/60s/40s off/on/off sessions), pressing a water-filled ball with the thumb and the index finger of the right hand. The ball was connected to a pressure transducer, in turn linked to a data acquisition card, allowing real-time analysis of the exerted pressure and delivery of an auditory feedback (desired force range being ±15% of the target level, which was, in turn, randomized on each pinch grip and varied between 4 and 7% of the subject's maximum voluntary contraction). Thereafter, medical air alternating with graded hypercapnia (up to 10%CO_2, 21% O_2 and balance N_2, which produced an average end-tidal CO_2 increase of 23±2 mmHg) was administered in 1min/3min/2min blocks. All the examinations were performed on a Siemens 1.5 T Magnetom Sonata system. The hypercapnic data were averaged across all subjects, at each CO_2 level, and a common maximum achievable BOLD signal change (M) was estimated by fitting of the averaged CBF data *vs.* averaged BOLD data to the deoxyhemoglobin dilution model [3]. The individual task-induced $CMRO_2$ changes were calculated using the estimated M and the measured BOLD and CBF data during the functional run [3].

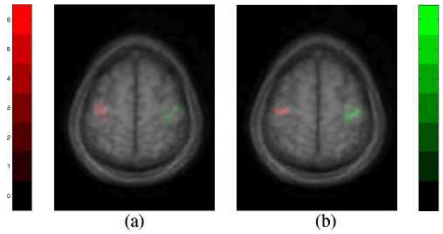

Figure 1: The BOLD (a) and CBF (b) ROIs (red for contra- and green for ipsilateral), transformed into the Talaraich space and summed over all subjects.

Results Task induced increases in BOLD signal were observed, contralaterally, in the primary sensorimotor cortex (SM1), premotor cortex (PMC), supplementary motor area (SMA), as well as as part of the posterior parietal association cortex (PPC) flanking the postcentral sulcus. Ipsilaterally, BOLD signal increased in the secondary areas (namely, PMC, SMA and PPC), but decreased in SM1. Figure 1 shows a slice of BOLD and CBF ROIs, summed over all subjects after registration with the Montreal Neurological Institute template brain. A typical set of BOLD signal and CBF time courses, in the ipsilateral M1 ROIs of a subject, is shown in Figure 2. Figure 3a displays the measured BOLD and CBF data pairs, for hypercapnic perturbation and motor task, as well as the calculated iso-$CMRO_2$ contours. In 7 out of 8 subjects, the magnitude of CBF and BOLD signal changes were significantly larger in the contra- than in the ipsilateral ROI. The maximum achievable BOLD signal increase (M) was 0.07±0.01 (with the χ^2 analysis indicating a good fit: q=0.37). The calculated $CMRO_2$ and the corresponding measured CBF changes, for each subject, are displayed in Figure 3b. The slope of the straight line fit to these data yielded a $CMRO_2$/CBF coupling ratio of 0.44±0.04 (with q of 0.98 indicating an excellent χ^2 fit).

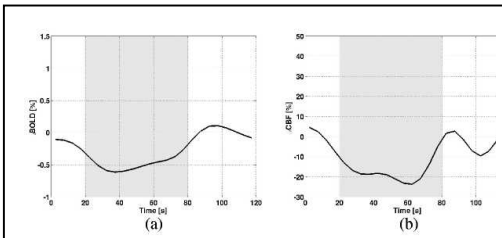

Figure 2: Time courses (low pass filtered, with FWHM=20s) of ipsilateral (negative) BOLD (a) and CBF (b) percent changes, averaged over all sessions, in a subject.

Conclusion We found a consistent linear relationship between oxygen consumption and perfusion in regions of sustained positive as well as negative BOLD response under normal physiological conditions. The slope of the linear fit to $CMRO_2$ *vs.* CBF changes from both ipsi- and contralateral ROIs was 0.44±0.04, in agreement with earlier motor studies investigating steady-state BOLD signal increases [4]. The current findings on the coupling between metabolic and hemodynamic processes underlying sustained BOLD decreases, in combination with extensive evidence on the accompanying neuronal inhibition from TMS experiments, provide support for steady-state negative BOLD response as a marker of neuronal deactivation.

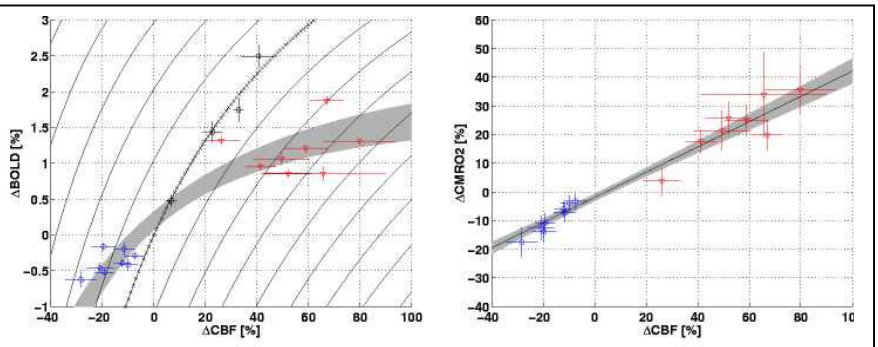

Figure 3: The changes in BOLD, CBF (left), and $CMRO_2$ (right) signals in the ipsi- ROIs (blue circles) and contralateral ROIs (red triangles) for each subject, with the average hypercapnia data shown as black squares.

References

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